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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,832	01/06/2005	Frank Karlsen	B0192.70051US00	8927

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,832	KARLSEN, FRANK	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 13-19* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/22/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: SEQ Notice

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group(s) I, claim(s) 1-9 and 13-19 in the reply filed on November 2, 2006 is acknowledged.

Claim(s) 10-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the

period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Page(s) 45-51, 53-57, 62, 63, and 88-91, respectively, contain sequences without SEQ ID NOs. Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Claim Rejections - 35 USC § 112 - Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim(s) 1-9 and 13-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The term "high-risk" in claim(s) 1-9 and 13-19 is a relative term which renders the claim indefinite. The term "high-risk" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification categorizes people from high-risk (no L1 expression, but E6 expression), to not as high risk (moderate risk) (L1 expression and E6 expression) (see sections 0028-0029). One cannot determine the delineation between what is deemed high,

moderate, and low-risk, especially when reading the claims in light of the specification, which suggests that there are different degrees of risks.

(b) Claim(s) 1-9 and 13-19 are indefinite because of the language "characterized in that" within claim(s) 1 and 2, as the scope is unclear. It is suggested that conventional U.S. claim language such as "wherein" be used in amended claims.

(c) Claim(s) 2 is further indefinite because the term "abnormal call changes in the cervix" renders the metes and bounds of the claim unclear. I cannot be determined what the claim considers abnormal cell changes. For example, is it cannot be determined if, for example, inflammation is considered an abnormal cell change.

(d) With regard to claim(s) 3, 4, 6, and 16 Applicant is requested to spell out the acronyms such as NASBA, ASCUS, etc. to avoid potential confusion.

(e) Claim(s) 8 and 18 are further indefinite because the term "preferably" renders the metes and bounds of the claim unclear. It cannot be determined whether the limitation following the term is part of the claimed invention.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for, "methods for *assessing the risk* of a patient to develop a cervical carcinoma" or "methods for *confirming the*

***diagnosis* of a cervical carcinoma in a patient" by screening for the expression of mRNA transcripts of the E6 gene of human papilloma viruses 16, 18, 31, 33, and 45 (HPVs), does not reasonably provide enablement for methods encompassing the *definitive diagnosis* of *any* abnormal cell changes in the cervix, nor methods encompassing screening the expression of mRNA transcript of the E6 gene HPVs other than 16, 18, 31, 33, and 45.**

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Enablement Issues

This scope of enablement rejection is based on several fundamental enablement problems with the claims. All of these issues are "how to use" problems in that the do not reasonably provide enablement for all claimed embodiments without undue experimentation. First, while the specification is enabling for "methods for *assessing the risk* of a patient to develop a cervical carcinoma" by screening for the expression of mRNA transcript of the E6 gene of HPV 16, 18, 31, 33, and 45, the specification does

not reasonably provide enablement for embodiments encompassing HPV 1-15, for example. Second, regarding claim(s) 2 and 13-19, the specification does not reasonably provide enablement for the claims as methods for the *definitive diagnosis* of *any* abnormal cell changes in the cervix.

The Nature of the Invention

The claims are drawn to a method for assessing the risk of a patient to develop a cervical carcinoma (e.g. claim 1) or a method for the diagnosis of abnormal cell changes in the cervix (e.g. claim 2). The invention is in the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of the Claims

The claims are broadly drawn to a method for assessing the risk of a patient to develop a cervical carcinoma (e.g. claim 1) or a method for the diagnosis of any abnormal cell changes in the cervix (e.g. claim 2) by screening for the expression of mRNA transcripts of the E6 gene of *any* HPV. Thus, the claims encompass the detection of mRNA transcripts of the E6 gene within a broad range of HPVs, such as HPV 1-15, for example, for the diagnosis of virtually any cell abnormality, including those other than carcinoma.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there is complete variability in the association of a particular HPV and the development of malignant cell tissue. It would require significant study and experimentation including trials with dozens of patients to determine that a type of disease is associated in any way with the methylation of a gene. This would be an inventive, unpredictable, and difficult undertaking in itself, as detection for any particular disease would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

State of the Art

The relationship between particular HPVs and their association with the development of certain cancers has been extensively studied for many years. It is well documented in the art, as demonstrated by the review article of Anderson ("Human Papillomavirus and Cervical Cancer" Clin. Microb. 2002 Aug;25(15):113-8), that only certain HPVs are associated with genital lesions (table 2, for example). Furthermore, it has been well established that only certain HPVs that are associated with genital lesions, carry a **high-risk** of cervical lesions and cancer (table 3, for example). Lastly, it has also been well established that **high-risk** HPV types can be distinguished from other HPV types based on the structure and function of the E6 gene product because the E6 protein has a high affinity for the p53 host gene products (pg. 115, col. 1-2, for example). Thus, the art suggests that the detection of mRNA transcripts of the E6 gene

of HPVs other than 16, 18, 31, 33, or 45 (e.g. HPV 1-15) is in no way an indication that the patient is at **high-risk** for the development of cervical cancer; in fact, the art clearly suggests that the opposite is true.

With specific regard to claim(s) 2 and 13-19, the art further suggests that the detection of any HPV is no way an indication that the patient *definitively* has abnormal cell changes at the time of detection. As Anderson highlights, "...cervical cancer develops in a multi-step process that most often takes **many years** and involves both presence of oncogene HPV genotypes and the interaction of many host factors,..., Several studies have shown that persistent infection with oncogenic viral types, such as HPV 16, is a very important determinant in the development of cervical cancer." Thus, the art suggests that the detection of mRNA transcripts of the E6 gene of HPVs 16, 18, 31, 33, or 45, while being an important factor in the diagnosis of cervical cancer, is in no way an indication that the patient *definitively* has abnormal cell changes at the time of detection. In fact, table 8 of the specification appears to indicate that biopsies of a negative cytology, in some instances, actually showed oncogenic E6 mRNA expression. Furthermore, no evidence could be found in the prior art that would indicate that the detection of mRNA transcripts of the E6 gene of HPVs would lead to an accurate and reliable determination of any abnormal cell change, such as inflammation.

Working Examples

The specification provides several working examples (pg. 59-88) of the claimed method, in which assays identified the oncogenic E6 expression assay HPVs 16, 18,

31, and 33 (pg. 82, lines 20-30, for example). The specification does not provide any evidence that detection of mRNA transcripts of the E6 gene of HPVs other than 16, 18, 31, 33, or 45 (e.g. HPV 1-15) is in any way an indication that the patient is at **high-risk** for the development of cervical cancer. Furthermore, the specification does not provide any evidence that detection of mRNA transcripts of the E6 gene of HPVs leads to an accurate and reliable determination of any abnormal cell change, such as inflammation.

Guidance in the Specification

Regarding claim(s) 1 and 3-9, the specification provides no scientific reasoning or evidence that detection of mRNA transcripts of the E6 gene of HPVs other than 16, 18, 31, 33, or 45 (e.g. HPV 1-15) is in any way an indication that the patient is at **high-risk** for the development of cervical cancer.

Claim(s) 2 and 13-19 specifically recite a method for the *definitive diagnosis* of abnormal cell changes in the cervix a patient, however, do not contain an active, definitive *diagnostic* step. Furthermore, at the time of filing, the specification does not provide any scientific reasoning or evidence that detection of mRNA transcripts of the E6 gene of any HPV definitely indicates that the patient has abnormal cell changes in the cervix. In fact, table 8 of the specification appears to indicate that biopsies of a negative cytology, in some instances, actually showed oncogenic E6 mRNA expression. "A method identifying human subjects having abnormal cell changes in the cervix" infers that the screening assay of E6 mRNA as claimed, done on a patient of unknown disease, was used to definitively diagnose a patient with abnormal cell changes in the

cervix, and requires that the evidence and subsequent diagnosis be thoroughly documented. In the instant case, the results are thoroughly documented, however, the results show that a definitely *reliable* method of identifying human subjects having abnormal cell changes in the cervix has not been established. In comparison, "A method for *assessing the risk* of a patient to develop a cervical carcinoma" or "A method for *confirming the diagnosis* of a cervical carcinoma in a patient" infers a much less degree of certainty as to whether the patient definitively has a particular type of colon cell proliferative disorder or a disorder at all, and thus requires much less evidence and of an actual diagnosis of the disease.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the art suggests that the detection of mRNA transcripts of the E6 gene of HPVs other than 16, 18, 31, 33, or 45 (e.g. HPV 1-15) is in no way an indication that the patient is at high-risk for the development of cervical cancer. While being enabling for, "methods for *assessing the risk* of a patient to develop a cervical carcinoma" or "methods for *confirming the diagnosis* of a cervical carcinoma in a patient" by screening for the expression of mRNA transcripts of the E6 gene of *certain* human papilloma viruses (HPVs), the specification does not reasonably provide one with the written description or guidance that leads one to a reliable method

where an association can be made between the expression of E6 mRNA from *any* HPV and the development of cervical cancer, or any abnormal cell change, as currently encompassed by the instant claims. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further, the specification does not provide guidance to overcome art and specification recognized problems in the use of methylation as prognostic of any disease state as broadly claimed.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence working examples which prove the unreliability of the methods, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to perform all the claimed embodiments of the method as broadly written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim(s) 1-9 and 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (WO 99/29890 A2; 17 June 1999) in view of Leone et al. ("Molecular beacon probes combined with amplification by NASBA enable homogeneous, real-time detection of RNA" Nucleic Acids Res. 1998 May 1;26(9):2150-5).

With regard to claim(s) 1 and 2, Lorincz teaches methods for assessing the risk of a patient with HPV to develop an HPV-based disease, e.g. the risk of a patient with HPV to develop malignant cancer (pg. 4-5, for example). Lorincz expressly teaches that the expression levels of E6 oncoproteins encoded by high-risk HPV types are a more sensitive and accurate measure of potential risk of an HPV infection developing into a cancerous lesion (pg. 7, for example).

Specifically, Lorincz an in vitro (pg. 11-19; example 2, for example method comprising: screening subjects (pg. 18, for example) for expression of mRNA transcripts of the E6 gene of HPV (example 2, for example); wherein the screening for E6 mRNA expression is carried out using isothermal amplification, such as NASBA (pg. 13, for example). Lorincz further outlines that certain HPV strains, e.g. 16 and 18 are associated with malignant cervical cancer (pg. 1-4, 7,13, for example). Lorincz does not expressly teach categorizing people based on expression results, however, given the fact that the disclosure makes specific reference to expression levels of E6 oncoproteins encoded by high-risk HPV in combination with certain HPV strains, e.g. 16

and 18 being associated with malignant cervical cancer, Lorincz clearly suggests such a method step.

With regard to claim(s) 3 and 13, Lorincz teaches NASBA (pg. 13, for example).

With regard to claim(s) 5, 5, 15, and 16, Lorincz teaches tissue from subjects known to have malignant cervical deposits (pg. 15-16,18,23, for example).

With regard to claim(s) 7-9 and 17-19, Lorincz teaches the detection of HPV 16 (pg. 23, for example).

Lorincz does not expressly teach or suggest the use of real-time amplification product detection.

Leone provides a supporting disclosure that teaches real-time monitoring of NASBA reactions utilizing molecular beacons (Pages 2151,2152, for example). They further teach that their methods allow for a truly homogeneous, timesaving assay in which amplification and detection of RNA can occur in one-tube (Page 2155, Column 1, Paragraph 3, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate molecular beacons into the amplification methods of Lorincz since Leone suggests such a modification to allow for amplification and detection of RNA in one-tube resulting in a reduction experimental time.

Conclusion

Claims 1-9 and 13-19 are rejected. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Cord (WO 01/73135 A2; 4 October 2001). Cord teaches methods for assessing the risk of a patient with HPV to develop an HPV-based disease analogous to that of Lorincz.

Smits et al. ("Application of the NASBA nucleic acid amplification method for the detection of human papillomavirus type 16 E6-E7 transcripts" J Virol Methods. 1995 Jul;54(1):75-81. Smits teaches NASBA of E6-E7 transcripts of cervical smears, however, does not specifically disclose real-time detection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

1/20/06

Christopher M. Babic
Patent Examiner
AU 1637

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10/500,832	Applicant(s) Karlsen
	Examiner Christopher M. Babic	Art Unit 1637

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1; 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See Office Action

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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